OPEN ACCESS Freely available online

ISSN: 0974-8369
Biology and Medicine

Review Article

DNA Hypomethylation in Chronic Non-Communicable Diseases

Claudia Rebolledo Quezada, Liliam Sanhueza Carrasco, Marcela Hinojosa-Moreno, Paulina Fernandez-Garces*

Department of Medicine, Medical Technologist, University of Concepción, Concepción, Chile

ABSTRACT

Genome methylation is a fundamental regulatory process of gene expression carried out by DNA Methyl Transferase enzymes (DNMTs), and constitutes one of the main epigenetic modifications. This modification is characterized for being stable and reversible, making it possible to establish global or gene-specific hypomethylation, which has been linked to alterations in physiological processes and the development of different pathologies. In this context, Chronic Non-Communicable Diseases (CNCD) have become important due to their high prevalence worldwide, and hypomethylation is highly evident in this kind of disease, which generates alterations in gene expression that are related to the onset and development of these diseases; therefore, it is fundamental to establish a relationship with the environment, which is able to influence epigenetics, making it possible to establish preventive measures for the establishment of CNCD.

Keywords: DNA methylation; Hypomethylation; Chronic non-communicable diseases; Cancer; Diabetes

Abbreviation's: DNMTs: DNA Methyltransferase Enzymes; CNCD: Chronic Non-Communicable Diseases; TET: Ten-Eleven Translocation Enzymes; CVD: Cardiovascular Diseases; SAM: S-adenosyl-L-Methionine; CpG: Cytosine phosphate-Guanosine Dinucleotides; 5mC: 5-methylCytosine; mESC: Mouse Embryonic Stem Cells; ESC: Embryonic Stem Cells; PCNA: Proliferating Cell Nuclear Antigen; TopIIα: Topoisomerase II α; miRNAs: microRNAs; 5hmC: 5-hydroxymethylCytosine; MMLV: Murine Leukemia Virus; PAHO: Pan American Health Organization; WHO: World Health Organization; PRMT6: Protein Arginine Methyltransferase 6; H3R2me2a: H3R2 Dimethylation; GWAS: Genome-Wide Association Studies; IR: Insulin Resistance; T2DM: Type 2 Diabetes Mellitus; IS: Ischemic Stroke; LAA: Large Arteries from Atherosclerotic Stroke; COPD: Chronic Obstructive Pulmonary Disease; AHRR: Aryl hydrocarbon Receptor Repressor Gene; DOHaD: Origins of Health and Disease Development; VEGFβ: Vascular Endothelial Growth Factor Receptor 2β; TNFα: Tumor Necrosis Factor α.

INTRODUCTION

Epigenetics is defined as the control of gene expression through mechanisms that do not modify the DNA sequence [1]. One of the main epigenetic modifications is methylation, which consists of the addition of a methyl group to the carbon five of a cytosine, a process that affects the regulation of gene expression [2,3]. For this process to take place, DNA MethylTransferase (DNMT) enzymes are required, which establish the genome methylation pattern in de novo methylation and are also in charge of maintaining this pattern during semiconservative DNA replication [4,5]. The reverse process, demethylation, is carried out by ten-eleven Translocation Enzymes (TET) [6]. Therefore, even though DNA methylation is considered a relatively stable modification, can be reversed by being influenced by environmental factors such as nutrition and chemical and industrial pollutants in addition to aging, being able to lead to the development of diseases such as cancer, obesity, diabetes, Cardiovascular Diseases (CVD), and respiratory diseases, among others [1,7,8].

Among the remodeling that the DNA methylation pattern undergoes in these situations, a loss of the methylated sites is included, causing hypomethylation of DNA, affecting numerous genomic regions, and representing a common feature of many tumors [8-10]. In the same context, since DNA methylation is susceptible to external stimuli, long-term changes in gene expression can be generated, which could lead to the development of pathologies contributing to the onset of Chronic Non-Communicable Diseases (CNCD) [11]. Approximately 22% of the world's population (from subjects under 20 years of age to those aged 70 years or older) suffer from at least one chronic disease [12]. CNCDs caused approximately 35 million deaths, representing 60% of all deaths, and NCDs constituted 80% of the global disease by 2020 [13]. The incidence of CNCDs has been increasing due to modifiable factors such as

Correspondence to: Paulina Fernandez-Garces, Department of Medicine, Medical Technologist, University of Concepción, Concepción, Chile, E-mail: paufernandezg@udec.cl

Received: 08-Oct-2022, Manuscript No. BLM-22-18246; **Editor assigned:** 11-Oct-2022, Pre QC No. BLM-22-18246 (PQ); **Reviewed:** 25-Oct-2022, QC No. BLM-22-18246; **Revised:** 01-Nov-2022, Manuscript No. BLM-22-18246 (R); **Published:** 08-Nov-2022, DOI: 10.35248/0974-8369.22.14.511.

Citation: Quezada CR, Carrasco LS, Moreno MH, Garces FP (2022) DNA Hypomethylation in Chronic Non-Communicable Diseases. Bio Med. 14:511.

exercise, diet, and smoking (factors that in turn impact genomic methylation patterns) [14,15]. However, only 1% of the world's resources are destined to prevent the CNCDs. Because of the great impact that triggers of these diseases have on genome methylation levels it is relevant to review CNCDs from the perspective of DNA hypomethylation, as this epigenetic phenomenon could be used as a biomarker to prevent, diagnose, or evaluate the prognosis of these pathologies [11,16]. This review details the processes of DNA methylation and demethylation as well as the hypomethylation present in the most prevalent chronic non-communicable diseases.

GENOME METHYLATION

In 1975, it was proposed that DNA methylation play a fundamental role in gene transcription, indicating that it constitutes the event responsible for the maintenance of a particular gene expression pattern through cell division [17,18]. Currently, DNA methylation is known as an important biological process characterized by being inheritable, stable, and reversibly essential for embryonic development and other phenomena, such as regulation of transcription, genomic imprinting, genome stability, X chromosome inactivation, and transcriptional repression [19-21] among other events.

In this process, a methyl group derived from S-Adenosyl-L-Methionine (SAM) covalently adheres to carbon 5 of a DNA base, specifically to the cytosine of Cytosine phosphate-Guanosine dinucleotides (CpG), thus transforming cytosine into 5-methylcytosine (5mC) [22]. Studies in mouse Embryonic Stem Cells (mESC) have shown that DNMTs are responsible for this process, and enzymes have been identified as DNMT3a and DNMT3b. Towards the end of the 90s, these enzymes were genetically inactivated in murine models, resulting in non-methylated DNA, causing lethality and multiple defects in the development of early embryos, indicating the role of these enzymes in de novo methylation of the genome during early embryogenesis. Later, in methylated genomic sequences from germ cells of murine and human models, it was observed that DNMT3a and DNMT3b interact directly with another DNMT, DNMT3L, which stimulates the activity of these enzymes and, therefore, DNA methylation [23,24].

On the other hand, Baubec et al. determined the genomic binding of DNMT3a and DNMT3b in mESC, showing that de novo DNMTs preferentially bind to regions of DNA rich in CpG sequences thus, approximately 80% of these dinucleotides are methylated in the genome, while the rest of the unmethylated CpG dinucleotides are mainly near promoter regions in dense clusters known as CpG islands, where the methylation percentage is less than 10% [25,26].

In mammals, three active DNMTs can be found in charge of regulating the methylation pattern: DNMT3a and DNMT3b, and the maintenance methyltransferase *DNMT1*, whose function is to maintain DNA methylation, copying the pattern in the strand of DNA synthesized during semi-conservative replication to maintain the cellular phenotype [27,28]. In Embryonic Stem Cells (ESC) as been shown, *DNMT1* enzyme forms complexes with the *UHRF1* protein and Proliferating Cell Nuclear Antigen (PCNA) in hemimethylated regions of DNA during replication [29]. However, in similar studies with ESC cell knock-out for the *UHRF1* gene, the location of hemimethylated sites by *DNMT1* has not been established, which shows the importance of *UHRF1* in maintaining DNA methylation owing to its ability to bind to methylated CpGs [29,30].

Additionally, mass spectrometry revealed that *UHRF1* and topoisomerase IIα (TopIIα) are co-expressed in hemimethylated zones [30]. Since the function of TopIIα in DNA copying is to decrease the tension on the replication fork, it was verified in mice with and without mutations in *UHRF1* that the interaction between these proteins is important in the recognition of the methylated DNA chain, giving *DNMT1* access to the complementary strand unmethylated cytosines [30,31].

Since DNA methylation is essential for the activation or repression of certain pathways and, therefore, for transcriptional regulation, this mark constitutes one of the main epigenetic modifications, together with the modification of histones and microRNAs (miRNAs) [32]. Pioneering studies on DNA methylation have considered this process irreversible; however, it is known that DNA demethylation is associated with the transcriptional repression of promoter regions and is a crucial step in determining cell fate in embryos and cell reprogramming. While DNA methylation is related to the suppression of gene expression, demethylation induces the reactivation and expression of genes [33,34].

Different studies postulate that enzymes of the TET family, TET-1 and TET-2, produce demethylation of the genome because its expression is correlated with a decrease in 5mC levels and an increase in its oxidized form, 5-hydroxymethylcytosine (5 hmC) [35-38]. This has been confirmed in HEK293 cells, which present an increase in 5hmC, 5-formylcytosine and 5-caboxylcytosine when overexpress TET-2 was overexpressed [39]. Furthermore, using murine transgenic lines, we studied the changes in level RNA messenger expression levels of TET and DNMT during global DNA demethylation and observed a gradual increase in the expression of TET1 and TET2 RNA messengers as DNA demethylates, while the genes encoding *DNMT1* and the associated protein *UHRF1* are constitutively expressed [40].

GENOME HYPOMETHYLATION

As mentioned above, because methylation is a reversible process, changes in the expression levels or mutations of the enzymatic machinery involved in genome methylation can lead to genomic hypomethylation, a phenomenon that can be reflected in the alteration of physiological processes, and therefore, in the development of diseases [41, 42].

Jia et al. described that the UHRF2 protein causes DNA hypomethylation by suppressing DNMT3a because an increase in methylation is observed in different knockdown cell lines for UHRF2. In general, the investigators observed that in mESC knock-out for DNMT3a/b or *DNMT1*, the reduced expression of UHRF2 significantly increased methylation ($p<0.05$), demonstrating that knockdown of UHRF2 or *UHRF1* resulted in an increase in the protein of DNMT3a and not in DNMT3b, both without variation at the mRNA level, concluding that *UHRF1/2* inhibits the methylation of de novo downregulating DNMT3a protein [43].

DNA hypomethylation involves the loss of the methyl group in genomic regions where it is normally present and is associated with aging, the development of non-communicable diseases, and tumor progression. It is frequently detected in human cancers due the loss of methylation would have a direct impact on the integrity of the chromatin, thus increasing genomic instability [44-47]. To investigate this phenomenon, Gaudet et al. (2003) generated mice carrying a hypomorphic allele of *DNMT1*, which reduced the expression of this enzyme by 10%, causing hypomethylation in all

tissues [48]. When comparing hypomethylated tumors and thymic murine leukemia virus (MMLV) tumors induced in transgenic mice, it was observed that 10 of the 12 hypomethylated tumors exhibited a gain in chromosome 15, while only two of the 12 induced MMLV tumors presented this trisomy, suggesting that hypomethylation plays a role in genomic instability during tumorigenesis. On the other hand, a case-control study carried out in 2017 by Shen et al. with 390 patients with glioma and 390 healthy patients evaluated the levels of methylation in leukocyte DNA using 5mC levels as a marker, showing that their levels were significantly lower in glioma cases than in healthy controls (3.45 vs. 3.82, p=0.001) [48,49]. In summary, it is possible to point out that the dysregulation of this epigenetic mark can initiate the development of various pathologies. Similarly, it has been observed that improvements in the quality of life have a positive impact on infectious diseases because their incidence decreases; however, CNCDs have had a contrary behaviour, shedding light on a permanent change in the expression of certain genes [50]. Today, CNCDs present a high prevalence worldwide, being responsible for around 80% of the deaths in America according to the Pan American Health Organization (PAHO), where the highest mortality rates are associated with cardiovascular diseases (150.7/100,000) and cancer (105.7/100,000), followed by other CNCDs such as diabetes and chronic respiratory diseases with an index higher than 30/100,000 [51].

GENOME HYPOMETHYLATION AND CANCER

Cancer is one of the main causes of morbidity and mortality from non-communicable diseases in the 21st century. In 2018, 9.6 million people worldwide perished from this pathology [52]. According to the World Health Organization (WHO), the three most common types of cancer are lung, breast and colorectal [53]. The disease is initiated by genetic and epigenetic alterations that lead to uncontrolled cell division, invasion, and metastasis [54]. Genomic hypomethylation was first described in 1983 when a decrease in 5mC was observed in human tumor tissues compared to normal tissues [55]. Subsequent studies have shown that hypomethylation is common in cancer and influences tumorigenesis in different types of cancer [56,57]. The tumorigenic capacity of the cells was evidenced by a plasmid pUP with regions of *DNMT1* capable of binding to PCNA and *UHRF1*, which prevented the formation of the *DNMT1/UHRF1* complex, which is necessary for the maintenance of methylation, and a decrease in 5mC levels was observed in the treated cells ($p<0.05$). Furthermore, the cells showed a decrease in their doubling times, and the apoptosis induced by irradiation and tumor formation was evidenced; therefore, the interruption of this complex and the consequent global hypomethylation is one of the main routes that contribute to the oncogenic phenotype favoring genomic instability and increased aneuploidy, classic hallmarks of cancer [57,58].

Furthermore, the large epigenetic changes observed in cancer may be the result of mutations in chromatin remodeling complexes that affect the homeostasis of DNA methylation, thus promoting the active or passive elimination of the methyl groups of cytosines, which could be a consequence of the dysregulated activation of members of the TET family or partial loss of function of DNMT proteins [59]. Thus, in cancer cell lines, an increase in *UHRF1/2* expression was observed, leading to global hypomethylation as a result of passive demethylation [43].

Similarly, overexpression of protein arginine methyltransferase 6 (PRMT6) was observed in bladder cancer samples compared to normal samples ($p<0.0001$). Veland et al. verified this increased expression in different human cancer cell lines and demonstrated in mESC clones with an overexpression of human PRMT6 that PRMT6 and its methyltransferase activity negatively regulate global DNA methylation, due PRMT6 is the enzyme responsible for asymmetric H3R2 dimethylation (H3R2me2a) and when evaluating the mESC, an increase in H3R2me2a is observed together with lower 5mC levels in relation to the control ($p<0.01$) [60,61]. Furthermore, ChIP experiments confirmed that the increase in H3R2me2a induced by the overexpression of PRMT6 deteriorates the association of *UHRF1* with chromatin, resulting in failure to maintain DNA methylation [61].

GENOME HYPOMETHYLATION IN OBESITY AND DIABETES

Obesity is currently considered a pandemic, the WHO notes that more than 1.9 billion adults are overweight and more than 650 million are obese, constituting a great burden on the global health system [62,63]. This disease is characterized by being highly heritable; however, through Genome-Wide Association Studies (GWAS), it has been shown that the genetic variants related to obesity have limited predictive power, in addition to the genetic component, it is influenced by epigenetic changes conditioned mainly by diet, particularly during pregnancy and childhood [64,65]. These trigger reprogramming of the germline epigenome, which increases the transmission of disease susceptibility to future generations through transgenerational epigenetic inheritance [63,64]. Using microarrays, Rhee et al. examined the levels of DNA methylation in peripheral leukocytes of 12 young, six obese, and six normal weight children, identifying 95.7% of differentially methylated CpG sites in transcriptional regions, highlighting low levels of DNA methylation in obese children compared to the control group [66].

Obesity can lead to serious conditions such as cardiovascular disease, osteoarthritis, non-alcoholic fatty liver disease, kidney disease, musculoskeletal disorders, some cancers, and Type 2 Diabetes Mellitus (T2DM) [64,67-69]. This last pathology is a disease of multifactorial origin, influenced by genetic predisposition and environmental factors such as diet and exercise [70-72]. In 2017, Thongsroy et al., using samples of patients classified as healthy patients, patients with T2DM, and patients with pre-DM, showed a decrease in methylation in Alu sites in samples from patients with DM compared to normal samples ($p<0.001$) [73].

In contrast, hepatic Insulin Resistance (IR) is a hallmark of T2DM. Nilsson et al. studied IR through the DNA methylation pattern of all liver genomes in people with T2DM and identified 251 CpG sites with differential DNA methylation in the liver of patients with T2DM, compared to non-diabetic subjects ($p<0.5$). These included CpG sites recorded in genes that are biologically relevant to the development of T2DM, such as GRB10, ABCC3, MOGAT1, and PRDM16 [74].

Additionally, Kirchner et al. carried out an analysis of the methyloma and transcriptome of the whole genome of the liver of people of the same age, classifying them as metabolically healthy non-obese, nondiabetic obese, and obese with T2DM, and discovered that the key genes involved in hepatic glycolysis and de novo lipogenesis were hypomethylated and activated in obese nondiabetic and obese patients with T2DM, compared to non-obese control subjects [71].

VanderJagt et al. conducted a longitudinal evaluation of the transition to 11 patients diagnosed with pre-DM to T2DM and observed a decrease in DNA methylated sites during progression to T2DM. They identified six genes (*SLC22A12*, *TRPM6*, *AQP9*, *HP*, *AGXT*, and *HYAL2*) hypomethylated in all patients, which are related to the development of diabetic nephropathy [75].

GENOME HYPOMETHYLATION AND CARDIOVASCULAR DISEASES

DNA methylation is involved in the processes underlying CVD, including atherosclerosis, inflammation, high blood pressure, and coronary heart disease [76-78]. Various studies have investigated the role of hypomethylation in CVD, and it has been observed that the key genes involved in the development of these pathologies are hypomethylated. Thus, Miao et al. showed that the *CXCL12* gene is hypomethylated in samples with coronary heart disease, increasing the expression of the gene, which is elevated in the inflammatory response, promoting the differentiation of endothelial cells to foam cells, causing vascular endothelial damage and, eventually, atherosclerosis, in this same line, Janssens et al., through association analysis of the epigenome of Large Arteries from Atherosclerotic stroke (LAA), identified 12 cases and 12 controls, a total of 1012 methylated CpG loci corresponding to 672 genes that presented a differential methylation pattern between LAA stroke cases and controls ($p<0.01$); of these, 438 CpG sites showed hypomethylation [79,80].

Hypomethylated genes are involved in both immune and metabolic functions. In parallel, it has been shown that MTRNR2L8 is hypomethylated in Ischemic Stroke (IS), obtaining a predictive value for the prognosis of this pathology [81]. Gallego et al. also studied differential methylation of CpG sites in patients treated with clopidogrel (an antiplatelet agent), 21 patients with recurrent vascular events, and 21 patients without vascular recurrence. During the first year of follow in patients with obtain vascular recurrence during treatment with Clopidogrel, was observed of lower levels in DNA methylation in *TRAF3* genes, which could indicate that hypomethylation of *TRAF3* gene may be directly related to vascular recurrence, independent of treatment with Clopidogrel [82].

GENOME HYPOMETHYLATION AND CHRONIC RESPIRATORY DISEASES

Chronic Obstructive Pulmonary Disease (COPD), bronchitis, allergic rhinitis, lung cancer. These pathologies have been related to changes in DNA methylation, with hypomethylation observed both in the global genome and in specific genes that give rise to and promote the progression of these pathologies [83-85]. Hypomethylation at CpG sites corresponding to IL-13 has been shown in patients with allergic rhinitis sensitized to house dust mites, a phenomenon associated with an increased risk of susceptibility to allergic rhinitis ($r=1.22$; $p=0.018$). In contrast, hypomethylation of the Aryl Hydrocarbon Receptor Repressor gene (AHRR) has been reported to be associated with respiratory diseases, being hypomethylated in smoking patients and in those with subsequent exacerbation of COPD and lung cancer. In addition, spirometry has studied the forced expiratory volume in 1 s and the forced vital capacity to assess lung function, observing that AHRR gene hypomethylation is associated with a decrease in the AHRR receptor in patients with respiratory symptoms [86,87].

As has been extensively studied, CS exposure to cigarette smoke is associated with respiratory pathologies. A study in A549 human lung adenocarcinoma cells exposed to cigarette smoke extracts and lipopolysaccharide showed significant global hypomethylation of DNA in relation to the control (p 0.0001), and blocking of the TET enzyme by antibodies showed that this enzyme is fundamental for the methylation changes that occur when exposed to cigarette smoke [85].

In conclusion, the presence of DNA hypomethylation in NCD (global or specific genes) leads to alterations in gene expression that may be related to the predisposition or development of these diseases.

DISCUSSION

Evidence indicates the presence of hypomethylated genes in different diseases which supports the idea that DNA hypomethylation induces changes in gene expression, representing one of the main components in the initiation and development of CNCD [42,45,70,73,75,88-90]. A crucial factor is nutrition, both in intrauterine life and in the first years of life, which is studied by the area "Origins of Health and Disease Development" (DOHaD) [91]. Various authors support the idea that early nutrition is one of the main causes of increased susceptibility to various pathologies, since it induces expression changes in key genes involved in different metabolic pathways during development [92-98]. Nutrients that affect SAM or SAH, inhibitors of methyltransferases, have the potential to modify methylation and, therefore, gene expression [98]. Among the first studies to initiate this idea is that conducted in 1998 in Dutch men and women born before, during and after the 1944-1945 Nazi famine, where it was shown that adults exposed to famine in half or late gestation had less glucose tolerance compared to those who were never exposed or were exposed in early gestation. Years later, Finer and his group evidenced alterations in the methylation of offspring exposed to gestational diabetes, which has a functional impact on placental endocytic processes and other extra and intracellular signalling pathways involved in growth and metabolism, while Ayonrinde et al., conversely, the duration of breastfeeding and the age of onset of supplemental formula milk consumption with the subsequent diagnosis of non-alcoholic fatty liver in adolescence [92,99,100]. In contrast, a study in murine models observed that a low-protein maternal diet during pregnancy and lactation promoted early onset glucose intolerance in offspring mice [101]. In this way, the environment influences epigenetics from intrauterine life, as the diet, both maternal and individual, is one of the reasons for the increase in the prevalence of these pathologies, for which nutri-epigenomics and nutri-epigenetics play a relevant role in the control of CNCDs [102].

The main objective of these disciplines is the effective design of personalized nutritional strategies that not only result in weight loss, but also contribute to preventing metabolic disorders such as T2DM, hypertension, dyslipidemia, and cardiovascular diseases [93]. Nutri-epigenetics is the study of how nutrition regulates the activation or deactivation of a specific gene, whereas nutri-epigenomics analyzes the interaction between various genes and nutrition, establishing those nutritional interventions can modify the epigenome and susceptibility to the development of diseases [103,104]. Considering this, it has been observed that dietary fatty acids can cause changes in methylation levels in gene promoters, such as vascular endothelial growth factor receptor 2β (VEGFβ) and Tumor Necrosis Factor α (TNFα), whose expression varies according to the type of fatty acid present in the diet, and can influence resistance to insulin, inflammatory processes, cardiovascular risk,

and DMT2 [104,105]. In addition, nutri-epigenomics is related to cancer, as low-folate diets have been associated with hypomethylation and an increased risk of pancreatic and colorectal cancer [1]. The study of nutri-epigenetics and nutri-epigenomics is fundamental, because personalized nutrition can prevent the development of CNCD.

DNA methylation is also indirectly affected by other environmental factors such as the economy, country of residence and education [91]. Taking relevance in addition to biological factors, socioeconomics, the current lifestyle in most of the world's population is characterized by a high consumption of fast food and ultra-processed foods, few hours of sleep, high levels of stress, and a sedentary lifestyle, which are responsible for the epidemic that today make up the ECNT.

In summary, global or specific gene hypomethylation constitutes an epigenetic marker highly prevalent in NCD, which is triggered by modifications in the DNA methylation pattern caused by genetic, environmental, and socioeconomic influences. Therefore, to overcome this burden on the health system, it is necessary to conduct multidisciplinary work, which includes political, medical, and scientific measures. The discovery of epigenetic markers allows considerable improvement in the approach to these pathologies, not only allowing a timely diagnosis, but also facilitating monitoring and providing new therapeutic options.

As it has been exposed in this review, DNA hypomethylation is one of the main epigenetic alterations responsible for the development of CNCDs, there being a vast group of hypomethylated genes present in various pathologies, which present functions that are altered and contribute to the onset and development of diseases. The current challenge, as new hypomethylated sites are identified, is to discriminate between hypomethylation marks, which influence pathophysiology and could constitute new epigenetic biomarkers useful for their early appearance in diseases and the association between molecular markers and lifestyle [16,38,90,106,107].

CONCLUSION

In addition, owing to its stability, frequency, reversibility, and accessibility in body fluids, it has great potential for the development of clinical trials to support the management of patients with CNCD, whether as an epigenetic biomarker for diagnosis, prognosis, resistance to treatment, or even because of its reversibility, can be established as a therapeutic objective. The development and application of epigenetic biomarkers are projected to be a promising line within the health system; however, it should be borne in mind that the priority of health services should focus on preventive measures for CNCDs, mainly through the empowerment of lifestyle changes.

DECLARATIONS

Ethical compliance

It is not applicable to this article because has not been worked with animals or people during the current review.

CONFLICT OF INTEREST

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

DATA ACCESS STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

FUNDING STATEMENT

This review was carried out under "Research Tutorial Course" in the Medical Technology career, of Faculty of Medicine in University of Concepción.

REFERENCES

1. Tiffon C. The impact of nutrition and environmental epigenetics on human health and disease. Int J Mol Sci. 2018;19(11):3425.
2. Zeng X, Yuan X, Cai Q, Tang C, Gao J. Circular Rna as an epigenetic regulator in chronic liver diseases. Cells. 2021;10(8):1945.
3. Gagliardi M, Strazzullo M, Matarazzo MR. DNMT3B functions: Novel insights from human disease. Front Cell Dev Biol. 2018;6:140.
4. Moore LD, Le T, Fan G. DNA methylation and its basic function. Neuropsychopharmacol. 2013;38(1):23-38.
5. Lyko F. The DNA methyltransferase family: A versatile toolkit for epigenetic regulation. Nat Rev Genet. 2018;19(2):81-92.
6. Ross SE, Bogdanovic O. TET enzymes, DNA demethylation and pluripotency. Biochem Soc Trans. 2019;47(3):875-885.
7. Horii T, Morita S, Hino S, Kimura M, Hino Y, Kogo H, et al. Successful generation of epigenetic disease model mice by targeted demethylation of the epigenome. Genome Biol. 2020;21(1):1-7.
8. Gensous N, Bacalini MG, Pirazzini C, Marasco E, Giuliani C, Ravaioli F, et al. The epigenetic landscape of age-related diseases: The geroscience perspective. Biogerontology. 2017;18(4):549-559.
9. Van Tongelen A, Loriot A, De Smet C. Oncogenic roles of DNA hypomethylation through the activation of cancer-germline genes. Cancer letters. 2017;396:130-137.
10. Abudawood M, Tabassum H, Almaarik B, Aljohi A. Interrelationship between oxidative stress, DNA damage and cancer risk in diabetes (Type 2) in Riyadh, KSA. Saudi J Biol Sci. 2020;27(1):177-183.
11. Sharp GC, Relton CL. Epigenetics and noncommunicable diseases. Epigenomics. 2017;9(6):789-791.
12. Di Ciaula A, Krawczyk M, Filipiak KJ, Geier A, Bonfrate L, Portincasa P. Noncommunicable diseases, climate change and iniquities: What COVID‐19 has taught us about syndemic. Eur J Clin Invest. 2021;51(12):13682.
13. Ndubuisi NE. Noncommunicable diseases prevention in low and middle-income countries: An overview of health in all policies (HiAP). Inquiry. 2021;58.
14. Bruins MJ, Van Dael P, Eggersdorfer M. The role of nutrients in reducing the risk for noncommunicable diseases during aging. Nutrients. 2019;11(1):85.
15. Plaza-Diaz J. Nutrition, microbiota and noncommunicable diseases. Nutrients. 2020;12(7):1971.
16. Berdasco M, Esteller M. Clinical epigenetics: Seizing opportunities for translation. Nat Rev Genet. 2019;20(2):109-127.
17. Holliday R, Pugh JE. DNA modification mechanisms and gene activity during development: Developmental clocks may depend on the enzymic modification of specific bases in repeated DNA sequences. Science. 1975;187(4173):226-232.
18. Riggs AD. X inactivation, differentiation, and DNA methylation. Cytogenet Genome Res. 1975;14(1):9-25.
19. Greenberg MV, Bourc'his D. The diverse roles of DNA methylation in mammalian development and disease. Nat Rev Mol Cell Biol. 2019;20(10):590-607.

20. Gong T, Gu X, Liu YT, Zhou Z, Zhang LL, Wen Y, et al. Both combinatorial K4me0-K36me3 marks on sister histone H3s of a nucleosome are required for Dnmt3a-Dnmt3L mediated de novo DNA methylation. J Genet Genomics. 2020;47(2):105-114.

21. Liang Z, Zhu Y, Long J, Ye F, Hu G. Both intra and inter-domain interactions define the intrinsic dynamics and allosteric mechanism in *DNMT1*s. Comput Struct Biotechnol J. 2020;18:749-764.

22. Liu SY, Shan NN. DNA methylation plays an important role in immune thrombocytopenia. Int Immunopharmacol. 2020;83:106390.

23. Okano M, Bell DW, Haber DA, Li E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. Cell. 1999;99(3):247-257.

24. Suetake I, Shinozaki F, Miyagawa J, Takeshima H, Tajima S. DNMT3L stimulates the DNA methylation activity of Dnmt3a and Dnmt3b through a direct interaction. J Biol Chem. 2004;279(26):27816-27823.

25. Baubec T, Colombo DF, Wirbelauer C, Schmidt J, Burger L, Krebs AR, et al. Genomic profiling of DNA methyltransferases reveals a role for DNMT3B in genic methylation. Nature. 2015;520(7546):243-247.

26. Luo C, Hajkova P, Ecker JR. Dynamic DNA methylation: In the right place at the right time. Science. 2018;361(6409):1336-1340.

27. Jeltsch A, Broche J, Bashtrykov P. Molecular processes connecting DNA methylation patterns with DNA methyltransferases and histone modifications in mammalian genomes. Genes. 2018;9(11):566.

28. Wong KK. *DNMT1*: A key drug target in triple-negative breast cancer. Semin Cancer Biol. 2021;72:198-213.

29. Sharif J, Muto M, Takebayashi SI, Suetake I, Iwamatsu A, Endo TA, et al. The SRA protein Np95 mediates epigenetic inheritance by recruiting *Dnmt1* to methylated DNA. Nature. 2007;450(7171):908-912.

30. Lu LY, Kuang H, Korakavi G, Yu X. Topoisomerase II regulates the maintenance of DNA methylation. J Biol Chem.2015;290(2):851-860.

31. Nitiss JL. DNA topoisomerase II and its growing repertoire of biological functions. Nat Rev Cancer. 2009;9(5):327-337.

32. Mittelstaedt NN, Becker AL, de Freitas DN, Zanin RF, Stein RT, Duarte de Souza AP. DNA methylation and immune memory response. Cells. 2021;10(11):2943.

33. Hill PW, Amouroux R, Hajkova P. DNA demethylation, Tet proteins and 5-hydroxymethylcytosine in epigenetic reprogramming: An emerging complex story. Genomics. 2014;104(5):324-333.

34. Kane AE, Sinclair DA. Epigenetic changes during aging and their reprogramming potential. Crit Rev Biochem Mol Biol. 2019;54(1):61-83.

35. Ito S, D'Alessio AC, Taranova OV, Hong K, Sowers LC, Zhang Y. Role of Tet proteins in 5 mC to 5 hmC conversion, ES-cell self-renewal and inner cell mass specification. Nature. 2010 ;466(7310):1129-1133.

36. Hackett JA, Sengupta R, Zylicz JJ, Murakami K, Lee C, Down TA, et al. Germline DNA demethylation dynamics and imprint erasure through 5-hydroxymethylcytosine. Science. 2013;339(6118):448-452.

37. Yuan EF, Yang Y, Cheng L, Deng X, Chen SM, Zhou X, Liu SM. Hyperglycemia affects global 5-methylcytosine and 5-hydroxymethylcytosine in blood genomic DNA through upregulation of SIRT6 and TETs. Clin Epigenetics. 2019;11(1):1-9.

38. Wang Z, Du M, Yuan Q, Guo Y, Hutchinson JN, Su L, et al. Epigenomic analysis of 5-hydroxymethylcytosine (5 hmC) reveals novel DNA methylation markers for lung cancers. Neoplasia. 2020;22(3):154-161.

39. Ito S, Shen L, Dai Q, Wu SC, Collins LB, Swenberg JA, et al. Tet proteins can convert 5-methylcytosine to 5-formylcytosine and 5-carboxylcytosine. Science. 2011;333(6047):1300-1333.

40. Bartoccetti M, van der Veer BK, Luo X, Khoueiry R, She P, Bajaj M, et al. Regulatory dynamics of Tet1 and Oct4 resolve stages of global DNA demethylation and transcriptomic changes in reprogramming. Cell reports. 2020;30(7):2150-2169.

41. Ciccarone F, Tagliatesta S, Caiafa P, Zampieri M. DNA methylation dynamics in aging: How far are we from understanding the mechanisms? Mech Ageing Dev. 2018;174:3-17.

42. Zhang W, Klinkebiel D, Barger CJ, Pandey S, Guda C, Miller A, et al. Global DNA hypomethylation in epithelial ovarian cancer: passive demethylation and association with genomic instability. Cancers. 2020;12(3):764.

43. Jia Y, Li P, Fang L, Zhu H, Xu L, Cheng H, et al. Negative regulation of DNMT3A de novo DNA methylation by frequently overexpressed UHRF family proteins as a mechanism for widespread DNA hypomethylation in cancer. Cell Discov. 2016;2(1):1-20.

44. Funaki S, Nakamura T, Nakatani T, Umehara H, Nakashima H, Okumura M, et al. Global DNA hypomethylation coupled to cellular transformation and metastatic ability. FEBS letters. 2015;589(24):4053-4060.

45. Zelic R, Fiano V, Grasso C, Zugna D, Pettersson A, Gillio-Tos A, et al. Global DNA hypomethylation in prostate cancer development and progression: A systematic review. Prostate Cancer Prostatic Dis. 2015;18(1):1-2.

46. Mutirangura A. Is global hypomethylation a nidus for molecular pathogenesis of age-related noncommunicable diseases? Epigenomics. 2019;11(6):577-579.

47. Dai X, Ren T, Zhang Y, Nan N. Methylation multiplicity and its clinical values in cancer. Expert Rev Mol Med. 2021;23.

48. Gaudet F, Hodgson JG, Eden A, Jackson-Grusby L, Dausman J, Gray JW, et al. Induction of tumors in mice by genomic hypomethylation. Science. 2003;300(5618):489-492.

49. Shen J, Song R, Gong Y, Zhao H. Global DNA hypomethylation in leukocytes associated with glioma risk. Oncotarget. 2017;8(38):63223.

50. Dagenais GR, Leong DP, Rangarajan S, Lanas F, Lopez-Jaramillo P, Gupta R, et al. Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): A prospective cohort study. Lancet. 2020;395(10226):785-794.

51. Organization PAH. NCDs at a glance: NCD mortality and risk factor prevalence in the Americas. 2019.

52. Rahman MM, Tollefsbol TO. Targeting cancer epigenetics with CRISPR-dCAS9: Principles and prospects. Methods. 2021 ; 187:77-91.

53. World Health Organization. Cancer.

54. Drake TM, Søreide K. Cancer epigenetics in solid organ tumours: A primer for surgical oncologists. Eur J Surg Oncol 2019; 45(5):736-746.

55. Gama-Sosa MA, Slagel VA, Trewyn RW, Oxenhandler R, Kuo KC, Gehrke CW, et al. The 5-methylcytosine content of DNA from human tumors. NAR. 1983; 11(19):6883-6894.

56. Sheaffer KL, Elliott EN, Kaestner KH. DNA hypomethylation contributes to genomic instability and intestinal cancer initiation. J Cancer Prev. 2016; 9(7):534-546.

57. Klein Hesselink EN, Zafon C, Villalmanzo N, Iglesias C, van Hemel BM, Klein Hesselink MS, et al. Increased global DNA hypomethylation in distant metastatic and dedifferentiated thyroid cancer. J Clin Endocr. 2018; 103(2):397-406.

58. Pacaud R, Brocard E, Lalier L, Hervouet E, Vallette FM, Cartron PF. The *DNMT1*/PCNA/*UHRF1* disruption induces tumorigenesis characterized by similar genetic and epigenetic signatures. Sci Rep. 2014; 4(1):1-9.

59. Baylin SB, Jones PA. Epigenetic determinants of cancer. Cold Spring Harb Perspect Bio. 2016; 8(9):019505.

60. Yoshimatsu M, Toyokawa G, Hayami S, Unoki M, Tsunoda T, Field HI, et al. Dysregulation of PRMT1 and PRMT6, Type I arginine methyltransferases, is involved in various types of human cancers. Int J Cancer 2011; 128(3):562-573.

61. Veland N, Hardikar S, Zhong Y, Gayatri S, Dan J, Strahl BD, et al. The arginine methyltransferase PRMT6 regulates DNA methylation and contributes to global DNA hypomethylation in cancer. 2017; 21(12):3390-3397.

62. Loh M, Zhou L, Ng HK, Chambers JC. Epigenetic disturbances in obesity and diabetes: Epidemiological and functional insights. Mol Metab. 2019; 27:33-41.

63. Obri A, Serra D, Herrero L, Mera P. The role of epigenetics in the development of obesity. Biochem Pharmacol. 2020; 177:113973.

64. King SE, Skinner MK. Epigenetic transgenerational inheritance of obesity susceptibility. Trends Endocrinol. Metab.. 2020; 31(7):478-494.

65. Samblas M, Milagro FI, Martínez A. DNA methylation markers in obesity, metabolic syndrome, and weight loss. Clin. Epigenetics. 2019; 14(5):421-444.

66. Rhee YY, Lee TH, Song YS, Wen X, Kim H, Jheon S, et al. Prognostic significance of promoter CpG island hypermethylation and repetitive DNA hypomethylation in stage I lung adenocarcinoma. Virchows Archiv. 2015; 466(6):675-683.

67. Dong L, Ma L, Ma GH, Ren H. Genome-wide analysis reveals DNA methylation alterations in obesity associated with high risk of colorectal cancer. Sci Rep. 2019; 9(1):1-11.

68. Nagashima M, Miwa N, Hirasawa H, Katagiri Y, Takamatsu K, Morita M. Genome-wide DNA methylation analysis in obese women predicts an epigenetic signature for future endometrial cancer. Sci Rep. 2019; 9(1):1-9.

69. Lin X, Li H. Obesity: Epidemiology, pathophysiology, and therapeutics. Front Endocrinol. 2021:1070.

70. Rönn T, Ling C. DNA methylation as a diagnostic and therapeutic target in the battle against Type 2 diabetes. NCBI. 2015; 7(3):451-460.

71. Kirchner H, Sinha I, Gao H, Ruby MA, Schönke M, Lindvall JM, et al. Altered DNA methylation of glycolytic and lipogenic genes in liver from obese and type 2 diabetic patients. Mol Metab. 2016; 5(3):171-183.

72. Cloete L. Diabetes mellitus: An overview of the types, symptoms, complications and management. 2021.

73. Thongsroy J, Patchsung M, Mutirangura A. The association between Alu hypomethylation and severity of type 2 diabetes mellitus. Clin. Epigenetics. 2017; 9(1):1-9.

74. Nilsson E, Matte A, Perfilyev A, de Mello VD, Käkelä P, Pihlajamäki J. et al. Epigenetic alterations in human liver from subjects with type 2 diabetes in parallel with reduced folate levels. J Clin Endocr. 2015; 100(11):1491-1501.

75. VanderJagt TA, Neugebauer MH, Morgan M, Bowden DW, Shah VO. Epigenetic profiles of pre-diabetes transitioning to type 2 diabetes and nephropathy. World J Diabetes. 2015; 6(9):1113.

76. Zhong J, Agha G, Baccarelli AA. The role of DNA methylation in cardiovascular risk and disease: methodological aspects, study design, and data analysis for epidemiological studies. Circ. 2016; 118(1):119-131.

77. Li Z, Yu F, Zhou X, Zeng S, Zhan Q, Yuan M, et al. Promoter hypomethylation of microRNA223 gene is associated with atherosclerotic cerebral infarction. Atherosclerosis. 2017; 263:237-243.

78. Deng Q, Huang W, Peng C, Gao J, Li Z, Qiu X, et al. Genomic 5-mC contents in peripheral blood leukocytes were independent protective factors for coronary artery disease with a specific profile in different leukocyte subtypes. Clin Epigenetics. 2018; 10(1):1-1.

79. Janssens R, Struyf S, Proost P. The unique structural and functional features of *CXCL12*. Cell Mol Immunol. 2018;15(4):299-311.

80. Miao L, Yin RX, Zhang QH, Hu XJ, Huang F, Chen WX, et al. Integrated DNA methylation and gene expression analysis in the pathogenesis of coronary artery disease. Albany NY. 2019;11(5):1486.

81. Shen Y, Peng C, Bai Q, Ding Y, Yi X, Du H, et al. Epigenome-wide association study indicates hypomethylation of MTRNR2L8 in large-artery atherosclerosis stroke. Stroke. 2019; 50(6):1330-1338.

82. Gallego-Fabrega C, Carrera C, Reny JL, Fontana P, Slowik A, Pera J, et al. *TRAF3* epigenetic regulation is associated with vascular recurrence in patients with ischemic stroke. Stroke. 2016 May; 47(5):1180-1186.

83. Song J, Heijink IH, Kistemaker LE, Reinders-Luinge M, Kooistra W, Noordhoek JA, et al. Aberrant DNA methylation and expression of SPDEF and FOXA2 in airway epithelium of patients with COPD. Clinical epigenetics. 2017; 9(1):1-0.

84. Yang IV, Pedersen BS, Liu AH, O'Connor GT, Pillai D, Kattan M, The nasal methylome and childhood atopic asthma. J Allergy Clin Immunol. 2017; 139(5):1478-488.

85. Kaur G, Batra S. Regulation of DNA methylation signatures on NF-κB and STAT3 pathway genes and TET activity in cigarette smoke extract–challenged cells/COPD exacerbation model in vitro. J. Biol.. 2020; 36(5):459-480.

86. Bojesen SE, Timpson N, Relton C, Smith GD, Nordestgaard BG. AHRR (cg05575921) hypomethylation marks smoking behaviour, morbidity and mortality. Thorax. 2017; 72(7):646-653.

87. Kodal JB, Kobylecki CJ, Vedel-Krogh S, Nordestgaard BG, Bojesen SE. AHRR hypomethylation, lung function, lung function decline and respiratory symptoms. Eur Respir J. 2018; 51(3).

88. Wolf C, Garding A, Filarsky K, Bahlo J, Robrecht S, Becker N, , et al. NFATC1 activation by DNA hypomethylation in chronic lymphocytic leukemia correlates with clinical staging and can be inhibited by ibrutinib. Int J Cancer. 2018; 142(2):322-333.

89. Choi IS, Estecio MR, Nagano Y, Kim DH, White JA, Yao JC, Hypomethylation of LINE-1 and Alu in well-differentiated neuroendocrine tumors (pancreatic endocrine tumors and carcinoid tumors). Mod Pathol. 2007; 20(7):802-810.

90. Nørgaard M, Haldrup C, Storebjerg TM, Vestergaard EM, Wild PJ, et al.Comprehensive evaluation of TFF3 promoter hypomethylation and molecular biomarker potential for prostate cancer diagnosis and prognosis. Int J Mol Sci. 2017; 18(9):2017.

91. Hoffman DJ, Reynolds RM, Hardy DB. Developmental origins of health and disease: current knowledge and potential mechanisms. Nutr Rev. 2017; 75(12):951-970.

92. Ayonrinde OT, Oddy WH, Adams LA, Mori TA, Beilin LJ, de Klerk N, et al. Infant nutrition and maternal obesity influence the risk of non-alcoholic fatty liver disease in adolescents. J Hepatol. 2017; 67(3):568-576.

93. Franzago M, Santurbano D, Vitacolonna E, Stuppia L. Genes and diet in the prevention of chronic diseases in future generations. Int J Mol Sci. 2020; 21(7):2633.

94. Gomez-Verjan JC, Barrera-Vázquez OS, García-Velázquez L, Samper-Ternent R, Arroyo P. Epigenetic variations due to nutritional status in early-life and its later impact on aging and disease. Clin Genet. 2020; 98(4):313-321.

95. Greco EA, Lenzi A, Migliaccio S, Gessani S. Epigenetic modifications induced by nutrients in early life phases: Gender differences in metabolic alteration in adulthood. Front Genet. 2019; 10:795.

96. Safi-Stibler S, Gabory A. Epigenetics and the developmental origins of health and disease: Parental environment signalling to the epigenome, critical time windows and sculpting the adult phenotype. Semin Cell Dev Biol 2020; 97:172-180. Academic Press.

97. Kadayifci FZ, Zheng S, Pan YX. Molecular mechanisms underlying the link between diet and DNA methylation. Int J Mol Sci. 2018; 19(12):4055.

98. Randunu RS, Bertolo RF. The effects of maternal and postnatal dietary methyl nutrients on epigenetic changes that lead to non-communicable diseases in adulthood. International Int J Mol Sci. 2020; 21(9):3290.

99. Ravelli AC, van der Meulen JH, Michels RP, Osmond C, Barker DJ, Hales CN, et al. Glucose tolerance in adults after prenatal exposure to famine. Lancet. 1998 ;351(9097):173-177.

100. Finer S, Mathews C, Lowe R, Smart M, Hillman S, Foo L, et al. Maternal gestational diabetes is associated with genome-wide DNA methylation variation in placenta and cord blood of exposed offspring. Hum Mol Genet. 2015; 24(11):3021-3029.

101. Zheng J, Xiao X, Zhang Q, Yu M, Xu J, Wang Z. Maternal protein restriction induces early-onset glucose intolerance and alters hepatic genes expression in the peroxisome proliferator-activated receptor pathway in offspring. J Diabetes Investig. 2015; 6(3):269-279.

102. Deodati A, Inzaghi E, Cianfarani S. Epigenetics and in utero acquired predisposition to metabolic disease. Front Genet 10:1270.

103. Joseph PV, Abey SK, Henderson WA. Emerging role of nutri-epigenetics in inflammation and cancer. Oncol Nurs Forum 2016; 43(6):784.

104. Monastero R, Garcia-Serrano S, Lago-Sampedro A, Rodriguez-Pacheco F, Colomo N, Morcillo S, Methylation patterns of Vegfb promoter are associated with gene and protein expression levels: the effects of dietary fatty acids. Eur J Nutr. 2017; 56(2):715-726.

105. García-Escobar E, Monastero R, García-Serrano S, Gómez-Zumaquero JM, Lago-Sampedro A. Dietary fatty acids modulate adipocyte TNFa production via regulation of its DNA promoter methylation levels. J Nutr Biochem. 2017; 47:106-112.

106. Costa-Pinheiro P, Montezuma D, Henrique R, Jerónimo C. Diagnostic and prognostic epigenetic biomarkers in cancer. Epigenomics. 2015; 7(6):1003-1015.

107. Wedge E, Hansen JW, Garde C, Asmar F, Tholstrup D, Kristensen SS, et al. Global hypomethylation is an independent prognostic factor in diffuse large B cell lymphoma. Am J Hematol. 2017; 92(7):689-694.